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Predicting survival in end-stage cystic fibrosis

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Summary
The natural history of cystic fibrosis (CF) is unpredictable and the optimal timing for lung transplantation in end-stage disease uncertain. Predicting survival based on FEV_1 alone remains controversial and therefore the aim of this study was to assess the value of walk test performance in pre-transplant assessment.

Retrospective review of adult patients with end-stage CF who underwent transplant assessment between 1988 and 2004 including a documented walk test on room air, but who died before transplant. The six-minute walk test (6MWT) was used between 1988 and 1993 and the shuttle walk test (SWT) thereafter, the two cohorts were therefore individually assessed.

A total of 121 patients were identified. The median (IQR) survival in patients performing SWT ($n = 77$) and 6MWT ($n = 44$) was 363 days (226, 566) and 433 days (232, 844), respectively, with survival in both cohorts significantly associated with pre-test (resting) heart rate (HR) ($p < 0.03$), but not distance walked, pre-test SpO_2, FEV_1 or BMI. It was predicted that 85% of patients performing SWT with a resting HR of 120 bpm, 70% of those with a HR of 109 bpm (cohort median) but only 25% with a HR of 72 bpm would die within 500 days. Distance walked in the SWT was significantly related to pre-test HR ($p < 0.01$), SpO_2 ($p < 0.01$) and Borg score ($p = 0.016$) when performing linear regression. Only pre-test HR remained significant when performing multiple regression.

Resting heart rate was the only consistent parameter in this study at predicting a high risk of dying on the transplant waiting list.

Abbreviations: BMI, body mass index; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HR, heart rate; IQR, interquartile range; PaO_2, arterial partial pressure of oxygen; $PaCO_2$, arterial partial pressure carbon dioxide; SpO_2, pulse oxygen saturation; SWT, shuttle walk test; 6MWT, six-minute walk test.

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Introduction

Predicted survival in patients with cystic fibrosis (CF) has doubled over the last 30 years from a median age of only 16 years in the early 1970's to over 32 years.[1] Respiratory failure remains the primary cause of mortality, with lung transplantation the only hope of improved survival.[2] The natural history of CF, however, remains unpredictable and with transplant waiting times increasing and donor organ availability in the UK decreasing, it is difficult to predict the optimal timing for assessment and transplantation in end-stage disease. A late referral puts the patient at risk of dying on a waiting list, but transplanting a patient too early puts the patient at significant risk from potential post-operative complications and may reduce overall survival.

Selection criteria for lung transplantation were introduced by an international consensus committee in 1998 (updated in 2006) based on lung function, arterial blood gas measurement and clinical characteristics.[3,4] However, predicting mortality and thereby identifying patients at high risk of dying on the waiting list utilising these parameters remains contentious.[4,5]

Walk tests provide a simple and reproducible measure of functional capacity in cardiorespiratory disease which may provide additional insight into those at greatest risk of dying whilst on a transplant waiting list.[6–11] In this retrospective study the utility of the incremental shuttle walk test, the six-minute walk test and resting clinical parameters performed as part of a pre-transplant assessment in patients with end-stage CF were evaluated.

Methods

This study has received a favourable opinion from the Royal Brompton and Harefield NHS Trust and National Heart and Lung Institute Ethics Committee.

Subjects

The medical records of all adult patients with end-stage CF who died whilst on the Royal Brompton and Harefield Hospital lung transplant waiting list between July 1988 and June 2004 were reviewed. Selection criteria for lung transplant assessment throughout the study period were consistent with the current guidelines.[3,4]

Functional data

Data collated included spirometry (Vitalograph; Buckingham, UK), arterial blood gas measurement on room air (Rapidlab™ 348; Bayer, UK) and body mass index as documented in the transplant assessment document.

Walk tests

Two walk tests have been utilised at the Royal Brompton Hospital since 1988, the six-minute walk test (6MWT) from 1988 to 1993 and the shuttle walk test (SWT) from 1994 to the present day. Walk tests have been performed as part of each patient's annual review as well as during transplant assessment over the last 15 years. Walk tests were not always repeated as part of the transplant assessment if they had been performed within three months as part of an annual review. Only data from patients performing walk tests on room air were included in the analysis. All patients were fully rested for at least 20 min before each test and were requested to withhold bronchodilators prior to the test. Heart rate was continuously monitored whilst sitting quietly during the rest period to achieve stability and during the walk test to record the highest heart rate.

The shuttle walk test

This constitutes a standardised incremental field exercise test described by Singh et al., which provokes a symptom limited maximal performance.[12] Patients are required to walk around a level 10 m course, defined by two cones along a hospital corridor. It is externally paced by a timed signal played on a cassette recorder and is progressive, increasing in speed every minute with the complete test lasting 12 min to a maximal possible distance of 1020 m. The end point of the test is determined either by the patient becoming too breathless to maintain the required speed, or by the operator when the patient fails to complete the shuttle in the time allowed (the patient is more than 0.5 m away from the cone when the signal sounds), or if oxygen saturation falls below 75%. Measurements recorded include distance walked (number of shuttles $\times$ 10 m), pre- and post-test oxygen saturations (SpO_2) using a hand-held oximeter (Nellcor NPB-40 from 1998, previously Nellcor N-200, Tyco Healthcare UK Ltd.), pre- and post-test heart rate and level of perceived breathlessness as measured by the Borg scale and subjective and objective recovery times.[13,14] Patients performing a SWT for the first time had a practice walk first with at least a further 45 min rest before the actual test.

The six-minute walk test

This test is based on the 12-min walk test described by McGavin et al.[15] Patients are instructed to walk around a level 30 m course defined by two cones along a hospital corridor for 6 min. In contrast to the SWT, patients walk at their own pace and can slow down or stop as necessary, with the distance walked recorded at the end of the test. However, at the end of the test patients should feel that they could not have walked any further in the time allowed. Measurements recorded include distance walked, pre- and post-test SpO_2 and heart rate. The Borg score was introduced at the same time as the SWT at this centre and therefore not available in patients performing the 6MWT. Patients performing a 6MWT for the first time had two practice walks at least 45 min apart.

Statistical analysis

In the analysis of the walk test data, survival was calculated from the date of the walk test whereas in the analysis of lung function, arterial blood gas measurement and BMI, survival was calculated from the date on the transplant assessment document as these were not necessarily performed on the same day.

Cox proportional hazards modelling was used to assess the effect of distance walked, pre-test heart rate, pre-test oxygen saturation (SpO_2) and pre-test Borg score (for SWT

only) on length of survival after the two exercise tests. In addition, regression analysis was used to see which markers were likely to affect the distance walked in the exercise tests.

Cox proportional hazards modelling was also used to assess the effect of lung function (FEV_1 and FVC), blood gas analysis (PaO_2, oxygen saturation and $PaCO_2$) and BMI on length of survival from the time of assessment.[16,17] All analysis was performed using Stata 9.2 (StataCorp, Texas).

Results

A total of 407 patients were accepted onto the transplant waiting list between 1988 and 2004, with 195 transplanted during this period (82 between 1988–1993, i.e. 6MWT cohort, and 113 between 1994–2004, i.e. SWT cohort). A total of 212 died on the waiting list during this period. Of the 212 patients, 146 patients had a documented walk test, of which 121 were performed without oxygen supplementation. Survival post-walk test, distance walked and pre- and post-test SpO_2 were available on all 121 patients.

Of these, 77 patients (35 male, 42 female, mean age 25 yrs) had a shuttle walk test and 44 patients (20 male, 24 female, mean age 23 yrs) had a six-minute walk test (Table 1).

Pre-test (resting) and post-test heart rate (HR), Borg scores, lung function data, arterial blood gas analysis and BMI in patients performing either SWT or 6MWT are also shown in Table 1. There was no significant difference in microbiological status between cohorts with >90% isolating *Pseudomonas*, 15% *Burkholderia* Cepacia Complex, 11% MRSA and 11% MSSA in the study group as a whole. Many had a mixed microbiological pattern.

Survival analysis

Post-shuttle walk test

Fig. 1 shows the Kaplan–Meier survival estimate for time to death of patients following the SWT. The median survival time was 363 days, with an interquartile range (IQR) between 226 and 566 days.

Cox proportional hazard modelling was performed on 30 patients for whom data on distance walked, pre-test HR, pre-test Borg score and pre-test SpO_2 were available. These four variables were included in the model. Analysis of the model residuals showed that the proportional hazards' assumptions were not violated.

Survival after the SWT was significantly associated with a patient's pre-test (resting) HR (Hazard ratio = 1.04, 95%CI: 1.01–1.07, $p = 0.02$). Distance walked and pre-test SpO_2 were not statistically significant when adjusted for pre-test HR. The median (IQR) pre-test HR was 109 (95, 122) bpm. Fig. 2 shows estimates of the survival function for arbitrary resting HR values of 72, 109 and 120 bpm. The effect of a resting tachycardia can clearly be seen. The Cox model predicts that almost 85% of patients with a resting HR of 120 bpm would have died by 500 days post-test. For patients with a resting HR similar to the median for this group i.e. 109 bpm, the model predicts that 70% would die before 500 days, but for patients with a relatively healthy resting HR of 72 bpm, only 25% would have died by this time point.

Post-six-minute walk test

Fig. 3 shows the Kaplan–Meier survival estimate for time to death of patients following the 6MWT. The shape of the curve is broadly similar to the shuttle walk test estimate, but the length of survival was longer in this group. Median survival time was 433 days with an interquartile range (IQR) between 232 and 844 days.

Pre-test HR data was only available for 8 patients in the 6MWT group. Therefore pre-test HR was not used in conjunction with any other model terms.[18] Two models were produced, one using only pre-test HR and another looking at distance walked and pre-test SpO_2. Neither model violated the proportional hazards' assumptions.

Survival after the 6MWT was also significantly associated with pre-test HR (Hazard ratio = 1.12; 95%CI: 1.01–1.24, $p = 0.028$). A separate model with distance walked and pre-test SpO_2 as the explanatory variables showed neither measurement had a significant effect on survival time. The

Table 1 Characteristics of patients performing a shuttle walk or six-minute walk test.

Patient characteristics	SWT		6MWT	
	Patient No	Median (IQR)	Patient No	Median (IQR)
Pre-test SpO_2 (%)	77	92 (89, 94)	44	89 (83, 92)
Post-test SpO_2 (%)	77	81 (76, 86)	44	79 (73, 85)
Walking distance (m)	77	300 (210, 385)	44	394 (240, 465)
Pre-test heart rate (bpm)	33	109 (95, 122)	8	120 (105, 136)
Post-test heart rate (bpm)	30	141 (132, 150)	8	146 (130, 155)
Pre-test Borg score	30	1 (0.5, 3.0)	na	na
Post-test Borg score	30	6 (4.5, 7.0)	na	na
FEV_1 predicted (%)	76	22 (19, 26)	44	18 (16, 23)
FVC predicted (%)	76	40 (32, 48)	44	33 (25, 41)
PaO_2 (kPa)	71	7.7 (6.9, 8.8)	41	7.3 (6.4, 8.3)
$PaCO_2$ (kPa)	71	5.8 (5.4, 6.5)	42	5.9 (5.3, 7.2)
BMI	71	17.2 (16.3, 18.8)	42	16.5 (15.5, 18.0)
Survival post-test (days)	77	363 (226, 566)	44	433 (232, 844)

na = not applicable.

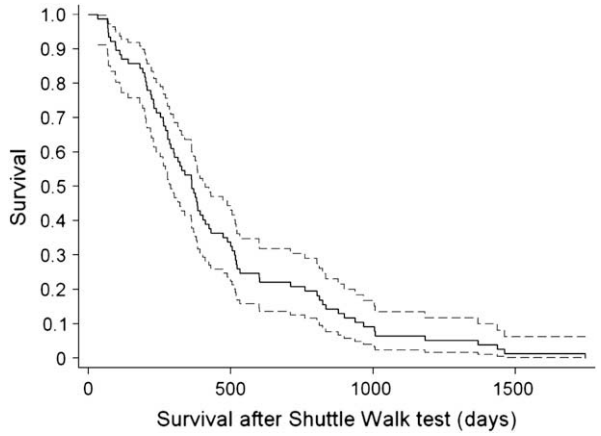

Figure 1 Kaplan–Meier survival estimate (- - - 95%CI) for time to death of patients following the shuttle walk test. Median survival 363 days (IQR 226, 566).

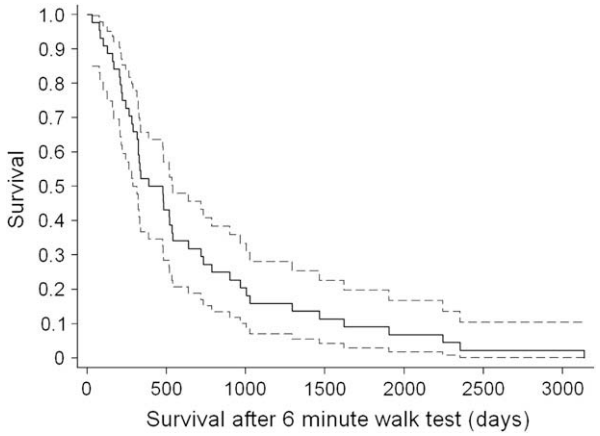

Figure 3 Kaplan–Meier survival estimate (- - - 95%CI) for time to death of patients following the six-minute walk test. Median survival 433 days (IQR 232, 844).

median (IQR) HR in this group of patients was 120 (103, 136). Fig. 4 shows Kaplan–Meier survival estimate post-six-minute walk test after splitting real observed data into two groups above and below the median (due to limited data). Even with the small amount of data available when assessing the effect of HR on survival, there is a clear difference in the predicted survival time of the two groups, and this helps to corroborate the findings of the SWT data above.

Regression analysis for shuttle walk test

Distance walked in the SWT was significantly related to pre-test (resting) HR ($\beta = -4.73$; 95%CI: -7.5 to -1.95, $p < 0.01$) when linear regression was performed. Pre-test SpO_2 ($\beta = 15.04$; 95%CI: 7.69–22.34, $p < 0.01$) and pre-test Borg score ($\beta = -59.12$; 95%CI: 106.11 to -12.13, $p = 0.016$) were also significantly related to a patient's ability to walk further distances when performing linear regression. On performing multiple regression pre-test HR remained statistically significant ($\beta = -3.92$; 95%CI: -7.09 to -0.75, $p < 0.02$), whilst pre-test SpO_2 ($p = 0.06$) and pre-test Borg score ($p = 0.53$) were no longer significant at the 5% level. Fig. 5 shows the linear regression relationships between pre-test HR and SpO_2 with distance walked. Shown on the graph are the regression line and the 95% prediction interval.

Effect of lung function, blood gas analysis and BMI on length of survival from the time of transplant assessment

A significant association was observed between survival post-assessment and PaO_2 (Hazard ratio = 0.59; 95%CI: 0.35–0.98, $p = 0.041$) and arterial saturation (Hazard ratio = 1.19; 95%CI: 1.05–1.36, $p = 0.006$) on room air but not between survival and lung function or BMI at the time of assessment in patients performing SWT. There was a significant association between survival and FVC (Hazard ratio = 1.08; 95%CI: 1.01 to 1.15, $p = 0.027$), but not FEV_1 (Hazard ratio = 0.93; 95%CI: 0.85–1.01, $p = 0.08$) or any other parameter in patients performing 6MWT.

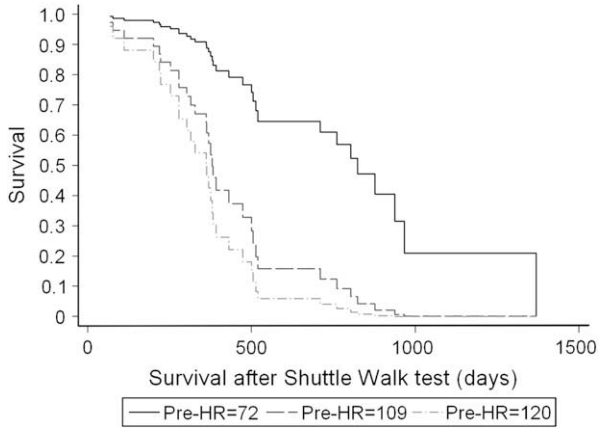

Figure 2 Estimates of the survival function post-shuttle walk test based on arbitary resting heart rate (HR) values of 72, 109 (cohort median) and 120 bpm. The cox model predicts that 85% of patients with a resting HR of 120 bpm, 70% with a HR of 109 bpm but only 25% with a HR of 72 bpm would have died by 500 days.

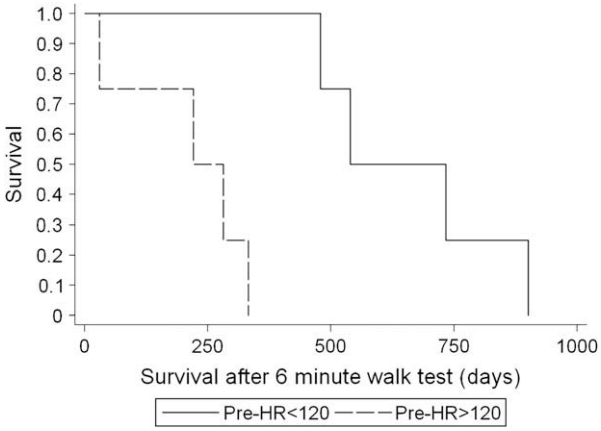

Figure 4 Kaplan–Meier survival estimate post-six-minute walk test after splitting real observed data into two groups above and below the median HR of 120 bpm. Despite small numbers a clear difference in survival is shown.

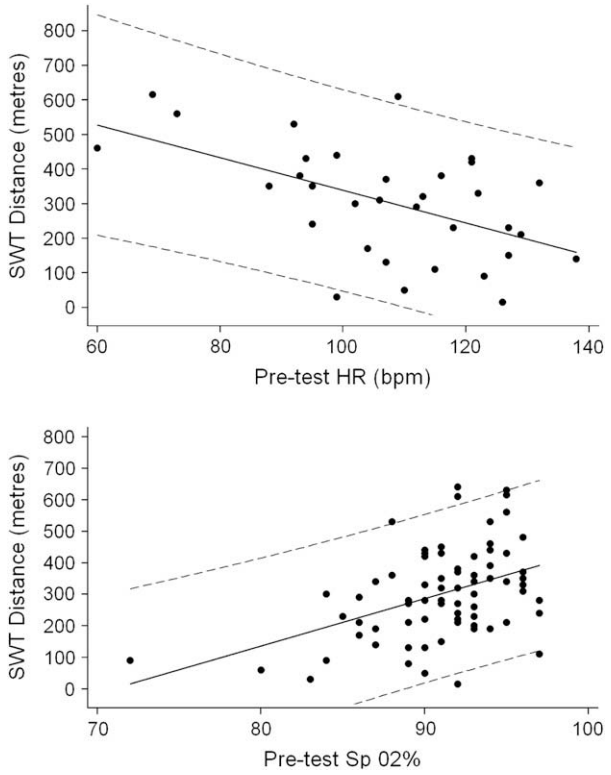

Figure 5 Linear regression relationship (- - - 95%CI) between pre-test heart rate (HR) and distance walked and pre-test oxygen saturation by pulse oximetry and distance walked on the shuttle walk test.

Discussion

In this study resting heart rate was the only consistent characteristic in predicting survival in end-stage cystic fibrosis (CF). An association between arterial oxygenation and survival was observed in the cohort performing SWT but not those performing 6MWT; and an association between FVC and survival in the cohort performing 6MWT but not those performing SWT. There was no association between distance walked and survival when adjusted for resting heart rate and no significant association between FEV_1 or BMI and survival in either cohort. Distance walked on SWT was associated with resting heart rate, oxygen saturation (as measured by pulse oximetry) and perceived level of breathlessness (Borg score) but only the association between heart rate and distance walked remained significant when performing multiple regression.

As a measure of functional capacity in cardiorespiratory disease an inverse relationship between resting sinus tachycardia and survival and between SWT distance and resting sinus tachycardia, hypoxia and Borg score is perhaps not surprising but provides support for the use of these parameters in the assessment of functional capacity in patients with CF. There was no additional prognostic value of utilising distance walked in walk tests in predicting survival as part of transplant assessment.

As the SWT is perhaps less dependent on patient motivation than the 6MWT it has been the preferred standard at the Royal Brompton Hospital since its introduction in 1993. It has been validated in patients with chronic obstructive airways disease (COPD), idiopathic pulmonary fibrosis and CF.[7,8,19,20] A significant correlation has been reported between resting PaO_2 and SWT performance in patients with idiopathic pulmonary fibrosis.[20] Peak oxygen consumption as measured by full cardiopulmonary exercise testing correlates with SWT distance in COPD and chronic heart failure, and is often considered a more optimal field exercise test than the 6MWT in predicting morbidity and mortality from cardiorespiratory disease.[11,21–23] Two previous SWT studies in patients with heart failure report a statistically significant cut off distance of 450 m, failure to achieve this identified cardiac patients with a high short term mortality.[11,24] A strong correlation between walking distance and survival has been reported by Rüter et al. in patients with end-stage CF performing a 12-min walk test.[10] Initial analysis of our SWT data in the same manner as Rüter et al. using Spearman's non-parametric correlation would also provide a significant, but in our study, weak correlation between walking distance and survival ($r = 0.24$, $p = 0.034$). However, no significant correlation could be demonstrated in patients performing a 6MWT and we were unable to confirm any association after adjusting for pre-test (resting) heart rate using the more robust statistical analysis of Cox proportional hazards modelling. As in our study, Rüter et al. also observed an association between resting oxygen saturation and distance walked but no association between FEV_1, $PaCO_2$ or BMI and survival, they also report a significant survival disadvantage of walking < 700 m.[10] Similarly, Kadikar et al. report that a walking distance of <400 m during a 6MWT identifies CF patients at increased risk of dying whilst on a transplant waiting list, but they included patients utilising supplemental oxygen during the walk test.[25] Supplemental oxygen may enable patients to walk further by alleviating symptoms of breathlessness and improving exercise capacity, a confounding variable and therefore only patients performing walk tests on room air were included in our study.

Patients undergoing assessment between 1988 and 1993 performed a 6MWT whilst those assessed thereafter performed a SWT. Advances in CF treatment and predicted survival during our observation period preclude any direct comparisons between these two cohorts, although patients in the earlier 6MWT cohort did in fact have a longer median survival (433 days) despite having slightly worse clinical characteristics than the later SWT cohort (363 days). Clearly, overall survival in terms of age at death has improved since 1988 but this is likely a result of new treatments delaying the need for transplant referral rather than having a significant impact on survival thereafter. Despite this the SWT data was collected over an 11-year period and the authors acknowledge that this long observation period is a major limitation to the study. Other limitations as a result of the retrospective nature of this study must also be taken into account including the limited resting HR data in the 6MWT cohort and the imprecision in defining the timing of the last dose of bronchodilator especially in relation to long-acting bronchodilators which may have had some carry over effect. All patients included were taking bronchodilators in one form or another, although they were all asked to refrain from using them before the test.

A large prospective multi-centre study in patients performing both a SWT and 6MWT would be required to provide both direct comparison between the two walk tests and provide sufficient data for multivariate analysis over a much shorter observation period.

International guidelines for the selection of lung transplant candidates are intended as a general statement and based on consensus rather than higher levels of evidence-based medicine.[3,4] They are disease specific and suggest that CF patients should be considered for referral if they have an $FEV_1 \leq 30\%$ predicted, or $FEV_1 \geq 30\%$ predicted if associated with rapid progressive clinical deterioration e.g., rapid fall in FEV_1, increasing hospitalisations and intravenous antibiotic requirement, major haemoptysis and/or increasing cachexia despite optimal medical management.[3,4] Resting hypoxia, $PaO_2 < 7.3$ kPa (55 mmHg) and hypercarpnia, $PaCO_2 > 6.7$ kPa (50 mmHg) were also identified as useful criteria based on a similarly predicted two-year mortality of >50%.[26] Similar guidelines were followed at the Royal Brompton Hospital throughout the study period, with selection criteria for transplantation after acceptance on the transplantation waiting list based on blood group, height and calculated thoracic capacity, then severity as well as organ availability rather than FEV_1 or other specific clinical characteristics.

FEV_1 alone remains a poor predictor of the need for referral for lung transplantation, with an $FEV_1 > 30\%$ a relatively sensitive predictor of two-year survival but an $FEV_1 < 30\%$ is a poor positive predictor of death.[5] A retrospective study of lung transplantation outcome in CF found no survival benefit of lung transplantation when selection criteria was based on $FEV_1 < 30\%$ alone.[27] A substantial number of patients survive for many years with an $FEV_1 < 30\%$ and thus referral criteria based solely on this criterion as reported by Doershuk et al. may adversely affect overall survival.[28] Although there was a possible effect of lung function on survival in the cohort performing 6MWT this was not observed in the cohort performing SWT. It has been suggested that the rate of decline in lung function is probably a better predictor of need for referral.[29]

An association between arterial oxygenation (PaO_2) and saturation at the time of assessment with survival was demonstrated in those performing a SWT but not those performing a 6MWT. In contrast, oxygenation as measured by pulse oximetry (SpO_2) on the day of the exercise test was not associated with survival in either cohort. These measurements are not directly comparable as the exercise test may have preceded transplant assessment by a number of months if performed as part of an annual review and not repeated for the transplant assessment.

It is clear that no single variable is predictive of mortality, although a recent validated predicted mortality model in 14,572 CF patients based on lung function and clinical characteristics including age, height, sputum microbiology, number of hospitalisations and home intravenous antibiotic courses found no additional benefit of this model over $FEV_1 < 30\%$ predicted alone.[5] In contrast, a model including the outcome of a 12-min walk test, resting heart rate, FEV_1, age and sex has been shown to be of some value in predicting the life expectancy of children with end-stage disease.[30]

The underlying cause of sinus tachycardia in end-stage CF is likely to be multi-factorial including the effects hypoxia, hypercarbia, systemic inflammation and pulmonary hypertension. Although cor pulmonale is invariably a pre-terminal finding there is evidence of subclinical RV dysfunction in end-stage CF.[31,32] Indeed, we have previously demonstrated a strong relationship between hypoxia and hypercarbia and right ventricular systolic and diastolic dysfunction in the setting of consistent tachycardia and increased cardiac output in this patient population.[31] Other factors to be considered include the presence of anaemia, chronic beta-agonist usage and the potential effects of autonomic neuropathy especially in those with CF-related diabetes.

Conclusions

It remains difficult to know when to list and subsequently transplant patients, as a result of the fine balance between the risk of dying on a waiting list and the post-operative risk of curtailing a patient's life. It is however, reasonable to consider patients for lung transplantation with an $FEV_1 < 30\%$ or fulfilling other criteria laid down by international consensus including rate of deterioration, arterial blood gas analysis, frequency of intravenous antibiotics, sputum microbiology and not least of all, quality of life. Acknowledging the limitations of this retrospective study resting heart rate was the only consistent parameter in predicting a high risk of dying while waiting for transplantation. It is appropriate, therefore, that clinicians should pay more attention to this parameter when assessing their patients.

Conflict of interest statement

The authors have no financial, personal, academic or intellectual conflicts of interest.

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